Is Acute heart failure a distinctive disorder? An analysis from BIOSTAT-CHF

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Table 1. Baseline characteristics by cohort and patient status

	Index Cohort		Validation Cohort	
Parameter	**Inpatient (N=1694)***	**Outpatient (N=822)***	**Inpatient (N=935)**	**Outpatient (N=803)**
Male sex	1217 (71.8%)*	629 (76.5%)*	582 (62.2%)	563 (70.1%)
Age, years	70.4 (61.0, 78.3)	70.0 (61.5, 77.2)	76.1 (67.5, 82.7)	73.8 (66.3, 80.0)
Caucasian race	1671 (98.6%)	818 (99.5%)	930 (99.5%)	798 (99.4%)
Primary etiology: Ischemic heart disease	720 (43.2%)	406 (50.3%)	622 (66.5%)	500 (62.3%)
Primary etiology: Hypertension	166 (10.0%)	90 (11.2%)	116 (12.4%)	69 (8.6%)
Primary etiology: Cardiomyopathy	403 (24.2%)	228 (28.3%)	56 (6.0%)	67 (8.3%)
Primary etiology: Valvular disease	153 (9.2%)	37 (4.6%)	70 (7.5%)	68 (8.5%)
Reason for hospitalization				
New onset of Heart Failure	624 (36.8%)*	78 (9.5%)*	..	..
HF hospitalization in last year	462 (27.3%)*	332 (40.4%)*	269 (29.3%)	191 (24.1%)
Atrial fibrillation	784 (46.3%)*	359 (43.7%)*	420 (45.3%)	340 (42.7%)
Myocardial infarction	605 (35.7%)	358 (43.6%)	469 (50.3%)	380 (47.4%)
PCI	341 (20.1%)	203 (24.7%)	179 (19.5%)	146 (18.3%)
CABG	289 (17.1%)	144 (17.5%)	154 (16.5%)	154 (19.2%)
Diabetes mellitus	583 (34.4%)*	236 (28.7%)*	326 (35.1%)	235 (29.4%)
COPD	304 (17.9%)*	132 (16.1%)*	206 (22.2%)	113 (14.2%)
Peripheral artery disease	204 (12.0%)	69 (8.4%)	179 (19.7%)	195 (24.8%)
Stroke	164 (9.7%)	69 (8.4%)	197 (21.2%)	118 (14.9%)
Hypertension	1064 (62.8%)	505 (61.4%)	572 (61.4%)	435 (54.4%)
Renal disease	520 (30.7%)	176 (21.4%)	453 (49.4%)	332 (41.8%)
Current malignancy	79 (4.7%)	18 (2.2%)	51 (5.5%)	28 (3.5%)
Pacemaker	127 (7.5%)	56 (6.8%)	57 (6.1%)	58 (7.2%)
ICD	135 (8.0%)	70 (8.5%)	24 (2.6%)	45 (5.6%)
Bi-ventricular pacer (CRT)	32 (1.9%)	17 (2.1%)	6 (0.6%)	21 (2.6%)
Bi-ventricular pacer (CRT) and ICD	102 (6.0%)	71 (8.6%)	16 (1.7%)	39 (4.9%)
Height, cm	170.0 (165.0, 177.0)	172.0 (166.0, 178.0)	168.0 (160.0, 176.0)	170.0 (161.0, 176.0)
Weight, kg	80.0 (69.0, 92.0)	81.0 (71.0, 91.0)	79.0 (67.0, 93.0)	82.0 (70.0, 95.0)
Body mass index, kg/m^2	27.2 (24.0, 30.9)	27.1 (24.2, 30.4)	27.7 (24.1, 32.2)	28.6 (25.1, 32.9)
Heart rate, bpm	79.0 (70.0, 92.0)	72.0 (64.0, 82.0)	75.0 (64.0, 88.0)	69.0 (60.0, 79.0)

	Index Cohort		Validation Cohort	
Parameter	**Inpatient (N=1694)***	**Outpatient (N=822)***	**Inpatient (N=935)**	**Outpatient (N=803)**
Systolic blood pressure, mmHg	120.0 (110.0, 135.0)	126.0 (112.0, 140.0)	118.0 (106.0, 134.0)	129.0 (115.0, 145.0)
Diastolic blood pressure	70.0 (64.0, 80.0)	80.0 (70.0, 85.0)	66.0 (58.0, 75.0)	71.0 (64.0, 79.0)
LVEF, %	30.0 (25.0, 37.0)	30.0 (25.0, 35.0)	43.0 (35.0, 52.0)	39.0 (31.0, 48.0)
Heart failure classification				
HFrEF (LVEF <40%)	1167 (79.0%)	652 (85.2%)	345 (41.4%)	381 (51.8%)
HFmrEF (LVEF 40- <50%)	187 (12.7%)	95 (12.4%)	209 (25.1%)	192 (26.1%)
HFpEF (LVEF ≥50%)	124 (8.4%)	18 (2.4%)	279 (33.5%)	162 (22.0%)
NYHA class				
Class I	31 (1.9%)	25 (3.1%)	6 (0.6%)	11 (1.4%)
Class II	456 (28.0%)	412 (50.6%)	235 (25.1%)	477 (59.5%)
Class III	874 (53.6%)	354 (43.4%)	477 (51.0%)	295 (36.8%)
Class IV	270 (16.6%)	24 (2.9%)	217 (23.2%)	19 (2.4%)
Extent of peripheral edema				
Not Present	477 (33.2%)	366 (55.1%)	204 (24.2%)	385 (54.9%)
Ankle	443 (30.9%)	189 (28.5%)	284 (33.7%)	199 (28.4%)
Below Knee	375 (26.1%)	99 (14.9%)	278 (33.0%)	97 (13.8%)
Above Knee	140 (9.8%)	10 (1.5%)	77 (9.1%)	20 (2.9%)
Pulmonary congestion				
No	579 (34.8%)	575 (73.4%)	292 (32.3%)	627 (83.7%)
Single base	219 (13.2%)	92 (11.7%)	59 (6.5%)	36 (4.8%)
Bi-basilar	864 (52.0%)	116 (14.8%)	554 (61.2%)	86 (11.5%)
Orthopnea	745 (44.1%)*	134 (16.3%)*	..	..
Rales >1/3 up lung fields	229 (21.2%)	19 (9.1%)	43 (11.1%)	7 (3.3%)
Elevated jugular venous pressure	435 (39.4%)*	119 (21.6%)*	281 (36.0%)	169 (24.5%)
Hepatomegaly	270 (16.0%)	88 (10.8%)	34 (3.9%)	26 (3.8%)
Aldosterone antagonists	913 (53.9%)	426 (51.8%)	274 (29.4%)	286 (35.8%)
ACEi/ARB	1170 (69.1%)	650 (79.1%)	587 (63.0%)	632 (79.1%)
Beta blocker	1356 (80.0%)	737 (89.7%)	644 (69.1%)	608 (76.1%)
Loop diuretics	1684 (99.4%)	820 (99.8%)	..	..
Diuretics	1692 (99.9%)	822 (100.0%)	920 (98.7%)	791 (99.0%)
Digoxin	320 (18.9%)	171 (20.8%)	171 (18.3%)	138 (17.3%)

	Index Cohort		Validation Cohort	
Parameter	**Inpatient (N=1694)***	**Outpatient (N=822)***	**Inpatient (N=935)**	**Outpatient (N=803)**
Hemoglobin, g/dL	13.20 (11.76, 14.40)	13.60 (12.40, 14.70)	12.60 (11.20, 14.20)	13.50 (12.50, 14.70)
Hematocrit, %	40.00 (36.00, 43.20)	40.90 (37.60, 44.60)	39.70 (35.50, 43.70)	41.60 (38.50, 44.80)
Creatinine, µmol/L	104.31 (85.75, 132.60)	99.89 (81.00, 123.70)	99.00 (79.00, 128.00)	95.00 (81.00, 120.00)
eGFR, mL/min/1.73m^2	58.60 (42.43, 75.79)	61.78 (46.95, 79.63)	57.91 (41.57, 77.35)	62.32 (45.82, 78.04)
Urea, mmol/L	12.10 (7.80, 19.50)	10.20 (7.40, 15.35)	9.00 (6.50, 12.90)	8.30 (6.50, 10.90)
Sodium, mmol/L	139.0 (137.0, 142.0)	140.0 (138.0, 142.0)	139.0 (136.0, 141.0)	140.0 (138.0, 142.0)
Potassium, mmol/L	4.20 (3.86, 4.56)	4.30 (4.02, 4.70)	4.20 (3.90, 4.50)	4.40 (4.10, 4.70)
Phosphate, mmol/L	0.87 (0.70, 1.05)	0.85 (0.69, 1.03)	..	..
Albumin, g/L	32.0 (26.0, 36.0)	36.0 (30.0, 41.0)	35.0 (31.0, 39.0)	40.0 (37.0, 44.0)
Serum iron, µmol/L	7.0 (5.0, 11.0)	11.0 (7.0, 15.0)	9.0 (6.0, 13.0)	15.0 (11.0, 19.0)
Aldosterone, pg/mL	87.0 (38.0, 185.0)	109.0 (56.0, 215.0)	..	..
White blood cell count, 10^9/L	7.90 (6.50, 9.80)	7.60 (6.30, 9.00)	7.70 (6.20, 9.60)	7.20 (6.00, 8.85)
Renin, µIU/mL	92.39 (28.40, 287.64)	78.66 (28.80, 215.46)	..	..
Troponin T, pg/mL	36.40 (22.43, 62.34)	22.42 (14.53, 37.10)	43.81 (23.85, 99.00)	20.05 (13.46, 30.67)
Troponin I, pg/mL	15.59 (8.44, 36.61)	8.07 (4.84, 15.82)	..	..
NT-proBNP, pg/mL	3291.5 (1422.5, 6880.5)	1921.5 (734.6, 3890.0)	2361.0 (952.0, 5851.0)	777.0 (309.0, 1768.0)
GDF-15, pg/mL	3130.0 (1951.0, 5299.0)	2115.5 (1335.0, 3337.0)	3481.0 (2185.5, 5818.5)	2272.0 (1570.0, 3549.0)
ET-1, pg/mL	5.68 (4.30, 7.53)	4.70 (3.62, 6.13)	..	..
bio-ADM, pg/mL	36.89 (24.27, 59.50)	27.66 (19.95, 41.07)	32.1 (20.8, 52.3)	23.0 (16.6, 33.7)
IL-6, pg/mL	6.50 (3.65, 12.40)	3.20 (1.90, 5.70)	..	..
CA125, U/mL	64.40 (20.60, 169.00)	19.80 (12.00, 43.80)	44.95 (20.30, 123.50)	17.50 (12.00, 29.00)

Results are presented as frequency and percentage for discrete variables and as median, lower quartile (Q1), and upper quartile (Q3) for continuous variables.

*Result presented in Ferreira JP, Metra M, Mordi I, Gregson J, Ter Maaten JM, Tromp J, Anker SD, Dickstein K, Hillege HL, Ng L, van Veldhuisen DJ, Lang CC, Voors AA, Zannad F. Heart failure in the outpatient versus inpatient setting: findings from the BIOSTAT-CHF study. Eur J Heart Fail. 2019;21(1):112-20.

Table 2. Ability of selected biomarkers to discriminate between patients with worsening heart failure enrolled in the inpatient versus the outpatient setting

Parameter*	Effect size for a change of	Odds ratio (95% CI)	P-value	Optimal cutpoint	AUC/ Observed C-index	Sensitivity	Specificity	PPV	NPV
NT-proBNP, pg/mL, log2†	Doubling	1.32 (1.26, 1.39)	<.0001	9.2689 (616.90 pg/mL)	0.6395	0.9121	0.2182	0.7063	0.5466
NT-proBNP, log2 ≥9.2689‡	Yes vs. No	2.85 (2.24, 3.63)	<.0001	–	0.5640	0.9119	0.2162	0.7057	0.5435
NT-proBNP ≥400 pg/mL‡	Yes vs. No	2.64 (1.98, 3.51)	<.0001	–	0.5421	0.9400	0.1442	0.6936	0.5384
NT-proBNP (Olink)*	1	1.48 (1.37, 1.59)	<.0001	1.3156	0.6404	0.9175	0.2080	0.7049	0.5528
CA125, U/mL, log2†	Doubling	1.50 (1.42, 1.58)	<.0001	3.9078 (15.01 U/mL)	0.6983	0.8388	0.3680	0.7324	0.5256
CA125, log2 ≥3.9078‡	Yes vs. No	2.95 (2.40, 3.62)	<.0001	–	0.6017	0.8344	0.3690	0.7316	0.5195
CA125 ≥100 U/mL‡	Yes vs. No	4.25 (3.31, 5.46)	<.0001	–	0.6278	0.3832	0.8725	0.8610	0.4070
MUC-16 (Q8WXI7) †	1	1.58 (1.48, 1.69)	<.0001	4.8067	0.7118	0.8836	0.3028	0.7251	0.5666
ST2 (Q01638) †	1	1.84 (1.65, 2.04)	<.0001	2.4867	0.6629	0.9162	0.1861	0.700	0.5471
Troponin T, pg/mL, log2†	Doubling	1.80 (1.65, 1.96)	<.0001	3.8178 (14.10 pg/mL)	0.6837	0.9174	0.2436	0.7143	0.5889
Troponin T, log2 ≥3.8178‡	Yes vs. No	3.52 (2.76, 4.47)	<.0001	–	0.5794	0.9168	0.2420	0.7137	0.5852
Troponin I, pg/mL, log2†	Doubling	1.47 (1.38, 1.56)	<.0001	2.1205 (4.35 pg/mL)	0.6800	0.9198	0.2302	0.7120	0.6055
Troponin I, log2 ≥2.1205‡	Yes vs. No	2.91 (2.26, 3.76)	<.0001	–	0.5609	0.9204	0.2013	0.7037	0.5510
GDF-15, pg/mL, log2†	Doubling	1.72 (1.58, 1.88)	<.0001	10.0676 (1073.12 pg/mL)	0.6584	0.9443	0.1536	0.6969	0.5722
GDF-15, log2 ≥10.0676‡	Yes vs. No	2.83 (2.11, 3.80)	<.0001	–	0.5450	0.9423	0.1477	0.6950	0.5540
GDF-15 (Q99988) †	1	1.74 (1.58, 1.91)	<.0001	3.9365	0.6535	0.8966	0.2611	0.7147	0.5524
bio-ADM, pg/mL, log2†	Doubling	1.71 (1.55, 1.88)	<.0001	3.2218 (9.33 pg/mL)	0.6389	0.9893	0.0231	0.6762	n/a
bio-ADM, log2 ≥3.2218‡	Yes vs. No	1.43 (0.63, 3.22)	0.3914	–	0.5025	0.9885	0.0164	0.6744	0.4088

Parameter*	Effect size for a change of	Odds ratio (95% CI)	P-value	Optimal cutpoint	AUC/ Observed C-index	Sensitivity	Specificity	PPV	NPV
ADM (P35318) †	1	1.48 (1.34, 1.63)	<.0001	1.3221	0.6377	0.9999	0.0004	0.6734	n/a

Results from logistic regression models, modeling the probability for inpatient.
*Parameters followed by a UniProt ID were measured on Olink. The remainder were measured using Singulex assays.
†Model parameters and optimal cut-point allowed to vary and averaged across imputation datasets.
‡Same cut-point applied in each imputation dataset and resulting parameters averaged across imputation datasets.

Table 3. Backward selection results Inpatient vs. Outpatient

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Age, years	5	0.93 (0.88, 0.97)	0.0017	0.94 (0.89, 0.98)	0.0100	0.89 (0.83, 0.95)	0.0008
LVEF, %	5	1.08 (1.03, 1.15)	0.0050	1.10 (1.04, 1.17)	0.0009	1.11 (1.04, 1.20)	0.0040
Diastolic blood pressure ≤ 70 †	5	0.70 (0.62, 0.79)	<.0001	0.69 (0.61, 0.78)	<.0001	0.74 (0.64, 0.85)	<.0001
Diastolic blood pressure > 70 †	5	0.96 (0.90, 1.01)		0.97 (0.91, 1.03)		1.00 (0.93, 1.08)	
Heart rate, bpm	5	1.11 (1.08, 1.15)	<.0001	1.11 (1.07, 1.15)	<.0001	1.10 (1.05, 1.14)	<.0001
Albumin, g/L	1	0.88 (0.86, 0.91)	<.0001	0.92 (0.90, 0.94)	<.0001	0.93 (0.91, 0.96)	<.0001
Aldosterone, pg/mL, log2	Doubling	0.91 (0.86, 0.97)	0.0023				
ALT, U/L, log2	Doubling	1.25 (1.10, 1.42)	0.0007	1.28 (1.12, 1.46)	0.0004		
Hepcidin, nmol/L, log2	Doubling	1.17 (1.10, 1.24)	<.0001	1.09 (1.03, 1.16)	0.0041		
Serum iron, µmol/L, log2	Doubling	0.68 (0.58, 0.79)	<.0001	0.77 (0.66, 0.90)	0.0013		
Phosphate, mmol/L, log2	Doubling	3.42 (2.49, 4.69)	<.0001	3.30 (2.39, 4.56)	<.0001	2.28 (1.48, 3.49)	0.0002
sTfR, mg/L, log2	Doubling	1.38 (1.15, 1.65)	0.0005	1.48 (1.24, 1.77)	<.0001		
Total bilirubin, µmol/L, log2	Doubling	1.30 (1.10, 1.53)	0.0041				
Troponin T, pg/mL, log2	Doubling	1.44 (1.31, 1.60)	<.0001				
Potassium, mmol/L	1	0.68 (0.55, 0.83)	0.0002	0.67 (0.55, 0.82)	0.0002		
Transferrin, g/L	1	1.98 (1.45, 2.70)	<.0001				
Urea, mmol/L, log2	Doubling			1.31 (1.13, 1.53)	0.0007		
CA125, U/mL, log2	Doubling			1.25 (1.16, 1.35)	<.0001		
IL-6, pg/mL, log2	Doubling			1.26 (1.15, 1.38)	<.0001		
NT-proBNP, pg/mL, log2	Doubling			0.87 (0.81, 0.94)	0.0004	0.87 (0.78, 0.96)	0.0076
Troponin I, pg/mL, log2	Doubling			1.30 (1.21, 1.39)	<.0001	1.31 (1.20, 1.42)	<.0001
ADM (P35318)	1					0.70 (0.56, 0.87)	0.0014
AGRP (O00253)	1					2.28 (1.65, 3.16)	<.0001
BOC (Q9BWV1)	1					0.45 (0.28, 0.73)	0.0012
FABP2 (P12104)	1					0.75 (0.64, 0.89)	0.0010
FGF-21 (Q9NSA1)	1					0.77 (0.70, 0.86)	<.0001

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
GH (P01241)	1					0.75 (0.68, 0.83)	<.0001
SERPINA12 (Q8IW75)	1					1.22 (1.06, 1.40)	0.0058
FABP4 (P15090)	1					1.43 (1.22, 1.68)	<.0001
FAS (P25445)	1					0.45 (0.32, 0.62)	<.0001
GDF-15 (Q99988)	1					1.50 (1.15, 1.97)	0.0037
MMP-3 (P08254)	1					0.57 (0.47, 0.69)	<.0001
OPN (P10451)	1					1.55 (1.21, 1.98)	0.0006
ST2 (Q01638)	1					1.66 (1.33, 2.09)	<.0001
TR (P02786)	1					1.48 (1.18, 1.85)	0.0007
GPNMB (Q14956)	1					0.25 (0.11, 0.56)	0.0015
MUC-16 (Q8WXI7)	1					1.30 (1.17, 1.46)	<.0001
RET (P07949)	1					0.53 (0.42, 0.66)	<.0001
SYND1 (P18827)	1					2.13 (1.58, 2.86)	<.0001
TFPI-2 (P48307)	1					1.90 (1.43, 2.53)	<.0001
uPA (P00749) $\leq$ 3.9 †	1					0.31 (0.19, 0.48)	<.0001
uPA (P00749) > 3.9 †	1					0.72 (0.46, 1.11)	
CYR61 (O00622) $\leq$ 7.2 †	1					1.64 (0.92, 2.92)	0.0006
CYR61 (O00622) > 7.2 †	1					0.53 (0.38, 0.76)	
Hosmer-Lemeshow goodness-of-fit test			0.0741		0.0487		0.2342
Pooled C-index in Index Cohort		0.8194		0.8324		0.9133	
C-index of final model in Index Cohort		0.8191		0.8322		0.9126	
Bias-corrected C-index (95% CI) §		0.8262 (0.8195, 0.8330)		0.8378 (0.8312, 0.8444)		0.9205 (0.9139, 0.9270)	
Bias-corrected difference in C-index (95% CI) compared to Model 1 §				0.0116 (0.0059, 0.0173)		0.0942 (0.0863, 0.1022)	

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Bias-corrected difference in C-index (95% CI) compared to Model 2 [§]						0.0827 (0.0744, 0.0909)	
C-index of final model in Validation Cohort		0.8731		0.8716		0.9011	

Results from logistic regression model, modeling the probability for inpatient.

[†] *Non-linear association modeled as linear spline.*

[§] *Bootstrap estimate with 100 resampling steps.*

Table 4. Backward selection results for Death through Day 180 - Inpatients

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Age, years	5	1.15 (1.08, 1.24)	<.0001	1.11 (1.03, 1.19)	0.0042	1.13 (1.04, 1.22)	0.0031
Systolic blood pressure ≤ 125 mmHg †	10	0.83 (0.73, 0.95)	0.0075	0.85 (0.74, 0.97)	0.0301	0.83 (0.72, 0.95)	0.0017
Systolic blood pressure > 125 mmHg †	10	1.14 (1.03, 1.25)		1.11 (1.01, 1.23)		1.18 (1.07, 1.30)	
Albumin, g/L	1	0.97 (0.95, 0.99)	0.0007				
Hemoglobin, g/dL	1	0.92 (0.85, 1.00)	0.0389	0.91 (0.84, 0.99)	0.0245	0.86 (0.79, 0.94)	0.0009
FGF23, RU/mL, log2	Doubling	1.25 (1.15, 1.36)	<.0001				
NT-proBNP, pg/mL, log2	Doubling	1.31 (1.17, 1.46)	<.0001	1.20 (1.07, 1.35)	0.0019		
Renin, μIU/mL, log2	Doubling	1.17 (1.10, 1.24)	<.0001	1.16 (1.09, 1.24)	<.0001	1.14 (1.07, 1.23)	0.0002
Triglycerides, mmol/L, log2	Doubling	1.43 (1.02, 2.00)	0.0453				
Troponin T, pg/mL, log2	Doubling	1.18 (1.08, 1.30)	0.0004	1.17 (1.06, 1.29)	0.0015	1.14 (1.03, 1.26)	0.0088
Alkaline phosphatase, μg/L, log2	Doubling			1.30 (1.01, 1.67)	0.0452		
ET-1, pg/mL, log2	Doubling			1.49 (1.15, 1.93)	0.0024	1.45 (1.12, 1.87)	0.0044
Hepcidin, nmol/L, log2	Doubling			0.88 (0.82, 0.95)	0.0012	0.90 (0.84, 0.97)	0.0048
IL-6, pg/mL, log2	Doubling			1.11 (1.01, 1.23)	0.0323		
pro-ENK, pmol/L, log2	Doubling			1.45 (1.18, 1.77)	0.0003		
Transferrin, g/L	1			0.79 (0.64, 0.98)	0.0348		
Body mass index, kg/m^2	1					0.96 (0.93, 0.99)	0.0072
HDL, mmol/L	1					0.47 (0.27, 0.81)	0.0084
LDL, mmol/L	1					1.27 (1.06, 1.53)	0.0158
BNP (P16860)	1					1.13 (1.02, 1.26)	0.0253
DCN (P07585)	1					2.10 (1.43, 3.08)	0.0002
TFF3 (Q07654)	1					1.21 (1.01, 1.45)	0.0422
IL6 (P05231) #	6.39 vs. 5.52					1.33 (1.15, 1.54)	<.0001
	5.52 vs. 4.83					1.10 (0.97, 1.24)	

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
KRT19 (P08727) ≤ 3.2 †	1					0.67 (0.42, 1.08)	<.0001
KRT19 (P08727) > 3.2 †	1					1.67 (1.35, 2.06)	
Pooled C-index in Index Cohort		0.7973		0.7993		0.8281	
C-index of final model in Index Cohort		0.7969		0.7990		0.8280	
Bias-corrected C-index (95% CI) §		0.8090 (0.7942, 0.8238)		0.8114 (0.7965, 0.8263)		0.8485 (0.8336, 0.8634)	
Bias-corrected difference in C-index (95% CI) compared to Model 1 §				0.0024 (-0.0100, 0.0148)		0.0395 (0.0234, 0.0556)	
Bias-corrected difference in C-index (95% CI) compared to Model 2 §						0.0371 (0.0224, 0.0518)	

Results from Cox proportional hazards regression model.

† *Non-linear association modeled as linear spline.*

Non-linear association modeled as cubic polynomial. Effect sizes for 75th percentile vs. median and for median vs. 25th percentile are presented.

§ *Bootstrap estimate with 100 resampling steps.*

Table 5. Backward selection results for Death through Day 180 - Outpatients

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Age, years	5	1.32 (1.09, 1.60)	0.0046	1.22 (1.02, 1.46)	0.0263	1.23 (1.02, 1.48)	0.0329
Hypertension	Yes vs. No	0.42 (0.20, 0.88)	0.0217				
Myocardial infarction	Yes vs. No	2.14 (1.08, 4.26)	0.0300				
Peripheral artery disease	Yes vs. No	3.73 (1.52, 9.15)	0.0044				
LVEF ≤ 35 % †	1	0.94 (0.89, 0.99)	0.0240				
LVEF > 35 % †	1	1.06 (1.00, 1.11)					
Hemoglobin, g/dL	1	0.75 (0.60, 0.94)	0.0130	0.72 (0.57, 0.90)	0.0039	0.72 (0.57, 0.91)	0.0056
Potassium, mmol/L	1	2.05 (1.04, 4.05)	0.0407				
Platelet count, 10^9/L, log2	Doubling	4.88 (2.25, 10.61)	0.0001	3.90 (1.54, 9.88)	0.0069	3.59 (1.31, 9.83)	0.0186
Total bilirubin, µmol/L, log2	Doubling	2.05 (1.23, 3.42)	0.0098				
Male sex	Yes vs. No			4.12 (1.51, 11.26)	0.0060	4.47 (1.57, 12.70)	0.0051
CA125, U/mL, log2	Doubling			1.47 (1.21, 1.78)	0.0001	1.45 (1.21, 1.74)	<.0001
pro-ENK, pmol/L, log2	Doubling			1.88 (1.12, 3.14)	0.0213		
Red blood cell count, 10^{12}/L	1			1.90 (1.10, 3.30)	0.0259	1.94 (1.11, 3.39)	0.0235
CNTN1 (Q12860)	1					0.53 (0.29, 0.96)	0.0409
SCGB3A2 (Q96PL1)	1					1.81 (1.31, 2.52)	0.0005
Pooled C-index in Index Cohort		0.8277		0.8156		0.8460	
C-index of final model in Index Cohort		0.8244		0.8127		0.8428	

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**

Results from Cox proportional hazards regression model.
[†] Non-linear association modeled as linear spline.

Table 6. Backward selection results for HF re-admission through Day 180 - Inpatients

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Diabetes mellitus	Yes vs. No	1.33 (1.02, 1.74)	0.0373	1.33 (1.02, 1.74)	0.0373		
Myocardial infarction	Yes vs. No	1.75 (1.35, 2.27)	<.0001	1.75 (1.35, 2.27)	<.0001	1.87 (1.45, 2.41)	<.0001
Peripheral artery disease	Yes vs. No	0.66 (0.45, 0.98)	0.0386	0.66 (0.45, 0.98)	0.0386		
LVEF, %	1	1.02 (1.01, 1.03)	0.0043	1.02 (1.01, 1.03)	0.0043	1.02 (1.00, 1.03)	0.0118
Systolic blood pressure, mmHg	10	0.93 (0.87, 1.00)	0.0383	0.93 (0.87, 1.00)	0.0383	0.92 (0.87, 0.99)	0.0202
eGFR, mL/min/1.73m^2	1	0.99 (0.99, 1.00)	0.0199	0.99 (0.99, 1.00)	0.0199		
Sodium, mmol/L	1	0.96 (0.93, 0.99)	0.0070	0.96 (0.93, 0.99)	0.0070	0.95 (0.92, 0.97)	0.0002
Alkaline phosphatase, µg/L, log2	Doubling	1.37 (1.09, 1.73)	0.0084	1.37 (1.09, 1.73)	0.0084	1.29 (1.02, 1.63)	0.0383
Ferritin, µg/L, log2	Doubling	0.89 (0.81, 0.99)	0.0241	0.89 (0.81, 0.99)	0.0241	0.89 (0.81, 0.98)	0.0136
FGF23, RU/mL, log2	Doubling	1.13 (1.02, 1.24)	0.0181	1.13 (1.02, 1.24)	0.0181		
GDF-15, pg/mL, log2	Doubling	0.80 (0.67, 0.95)	0.0135	0.80 (0.67, 0.95)	0.0135		
NT-proBNP, pg/mL, log2	Doubling	1.28 (1.16, 1.42)	<.0001	1.28 (1.16, 1.42)	<.0001		
Renin, µIU/mL, log2	Doubling	1.15 (1.08, 1.22)	<.0001	1.15 (1.08, 1.22)	<.0001		
HDL, mmol/L	1					0.62 (0.40, 0.97)	0.0401
RAGE (Q15109)	1					1.61 (1.20, 2.17)	0.0018
REN (P00797)	1					1.22 (1.05, 1.42)	0.0084
NT-proBNP (NA) ≤ 3.2 †	1					1.74 (1.30, 2.32)	0.0003
NT-proBNP (NA) > 3.2 †	1					1.02 (0.88, 1.19)	
Pooled C-index in Index Cohort		0.7395		0.7395		0.7322	
C-index of final model in Index Cohort		0.7389		0.7389		0.7314	
Bias-corrected C-index (95% CI) §		0.7577 (0.7411, 0.7744)		0.7586 (0.7405, 0.7767)		0.7462 (0.7292, 0.7632)	

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Bias-corrected difference in C-index (95% CI) compared to Model 1 [§]				0.0009 (-0.0072, 0.0089)		-0.0115 (-0.0308, 0.0078)	
Bias-corrected difference in C-index (95% CI) compared to Model 2 [§]						-0.0124 (-0.0310, 0.0062)	
Results from Cox proportional hazards regression model. [†] *Non-linear association modeled as linear spline.* [§] *Bootstrap estimate with 100 resampling steps.*							

Table 7. Backward selection results for HF re-admission through Day 180 - Outpatients

		Multivariable Model 1 Local and central data		Multivariable Model 2 Local, central, and Singulex data		Multivariable Model 3 Local, central, Singulex, and Olink data	
Parameter	**Effect size for a change of**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
HF hospitalization in last year	Yes vs. No	1.69 (1.05, 2.72)	0.0318	1.85 (1.15, 2.99)	0.0119	1.77 (1.09, 2.87)	0.0202
Body mass index ≤ 25 kg/m^2 †	1	0.84 (0.74, 0.96)	0.0334	0.81 (0.71, 0.92)	0.0050	0.82 (0.72, 0.94)	0.0212
Body mass index > 25 kg/m^2 †	1	1.03 (0.97, 1.09)		1.02 (0.96, 1.09)		1.04 (0.98, 1.11)	
LVEF, %	1	1.03 (1.01, 1.05)	0.0066	1.03 (1.01, 1.06)	0.0016	1.05 (1.03, 1.08)	<.0001
Diastolic blood pressure	5	0.84 (0.76, 0.94)	0.0015	0.84 (0.75, 0.94)	0.0019		
Alkaline phosphatase, µg/L, log2	Doubling	1.55 (1.01, 2.37)	0.0481	1.57 (1.02, 2.41)	0.0428		
FGF23, RU/mL, log2	Doubling	1.32 (1.14, 1.53)	0.0003	1.29 (1.11, 1.49)	0.0008		
NT-proBNP, pg/mL, log2	Doubling	1.25 (1.06, 1.48)	0.0084				
ET-1, pg/mL, log2	Doubling			1.83 (1.17, 2.85)	0.0081		
Troponin I, pg/mL, log2	Doubling			1.16 (1.02, 1.33)	0.0285		
Systolic blood pressure, mmHg	10					0.82 (0.71, 0.94)	0.0040
Serum iron, µmol/L, log2	Doubling					0.73 (0.58, 0.94)	0.0138
ADAM-TS13 (Q76LX8)	1					0.33 (0.11, 0.95)	0.0411
VEGFD (O43915)	1					3.04 (1.62, 5.72)	0.0006
NT-proBNP (NA)	1					1.55 (1.27, 1.89)	<.0001
GIF (P27352) ≤ 9.4 †	1					0.81 (0.65, 1.02)	0.0060
GIF (P27352) > 9.4 †	1					2.33 (1.37, 3.97)	
Pooled C-index in Index Cohort		0.7966		0.7984		0.8234	
C-index of final model in Index Cohort		0.7960		0.7981		0.8231	

Results from Cox proportional hazards regression model.
† *Non-linear association modeled as linear spline.*

Figure 1 (Central Illustration). Differential protein expression in inpatients relative to outpatients

Presented is a volcano plot of differential protein expression showing the fold change, i.e. the ratio of average expression in inpatients to average expression in outpatients, versus the corresponding t-test p-value per protein and on logarithmic scales. Higher values on the y-axis indicate stronger statistical significance, values >0 on the x-axis indicate upregulation in inpatients, and values <0 on the x-axis indicate downregulation in inpatients. Significantly differentially expressed proteins have been labeled.